A FDA Perspective on Nanomedicine
Current Initiatives in the US

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FDA

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Outline

• Context
• Nanotechnology Task Force report summary
• Identification and considerations for FDA products relevant to nanomedicine
• Current activities within FDA’s Center for Drug Evaluation and Research
• New activities across FDA
FDA focus on Nanotechnology

- Increasingly used in products regulated by FDA
  - Drugs, medical devices, cosmetics, dietary supplements
  - Near term/future applications-food applications, targeted medical therapies, device materials
- FDA plays key regulatory role for Nanotechnology in US
- National priority for the US
FDA Development of the Nanotechnology Task Force

- **Scientific Issues:**
  - Understanding the interaction of nanoscale materials with biological systems
  - Adequacy of testing approaches

- **Regulatory Policy Issues:**
  - Ability to identify products that contain nanoscale materials
  - Scope of authority regarding evaluation of safety and effectiveness
Science Recommendation: Understanding biological interactions

• More knowledge needed about
  • biological interactions
  • detection and measurement
• In-house expertise and infrastructure should be strengthened
• Agency-wide regulatory-science coordination for nanoscale materials needed.
Science Recommendation:
Adequacy of testing approaches

• Current testing approaches to assess safety, effectiveness, and quality of products with nanoscale materials should be evaluated.

• Promote/participate in
  – Development of characterization methods and standards for nanoscale materials
  – Development of models for the behavior of nanoscale particles in-vitro and in-vivo.
Regulatory Policy Issue: Identification and Scope of products containing Nanomaterials

- Requesting submission of data and other information addressing the effects on product safety and effectiveness of nanoscale materials in products subject to FDA premarket authorization.
- Issue guidance requesting submission of information on whether and how the presence of nanoscale materials affects the manufacturing process.
- Issue guidance for products
  - Subject to premarket approval
  - Not subject to premarket approval
List of terms applicable to Nanomedicine

- Nanoparticle
- Polymeric nanoparticle platforms
- Dendrimer
- Liposomes
- Micelles
- Nanoemulsions
- Nanocrystal
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<th>Platforms</th>
<th>Trade Name</th>
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<td>DepoCyt</td>
<td>Lymphomatous meningitis</td>
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<td>Doxil</td>
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<td>Visudyne (verteporfin for injection)</td>
<td>Photodynamic therapy for age-related macular degeneration</td>
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<td>Micelle</td>
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<td>Estrasorb</td>
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<td>Taxotere</td>
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<td>Tricor</td>
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<td>Triglide</td>
<td>Hypercholesterolemia and hypertriglyceridemia</td>
<td>5/7/2005</td>
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<td>Megace ES</td>
<td>Anorexia, cachexia or an unexplained significant weight loss in AIDS patients</td>
<td>7/5/2005</td>
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<td>Rapamune</td>
<td>Immunosuppressant; The prophylaxis of organ rejection in patients receiving renal transplants</td>
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<td>Nanoparticle</td>
<td>Abraxane</td>
<td>Metastatic breast cancer</td>
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<td>Anthelios 20</td>
<td>Sunscreen</td>
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<td>Helioblock SX Sunscreen Cream</td>
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<td>Somatuline depot</td>
<td>Acromegaly</td>
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<td>Superparamagnetic iron oxide</td>
<td>Feraheme Injection</td>
<td>Treatment of iron deficiency anemia in patients with Chronic Kidney Disease (CKD)</td>
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<td>Feridex</td>
<td>MRI contrast agent</td>
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<td></td>
<td>GastroMARK</td>
<td>Imaging of abdominal structures</td>
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Considerations for nanomaterial-containing drug products

- **Product quality assessment**
  - Characterization
  - Quality control
  - Manufacturing

- **Product safety assessment**
  - Biodistribution
  - Clearance
  - Metabolism
  - Toxicology
Characterization Questions

- Identification of products containing nanomaterials
- Identification of critical properties requiring characterization, for optimal product quality and performance assessment.
- Use of appropriate tools and methodologies to:
  - Adequately assess chemistry and any unique characteristics of products containing nanomaterials, using the complete formulation.
  - Use of appropriate quality control measures in order to produce consistent formulations with low batch-to-batch variability.
Safety Questions

• Physico-chemical properties of nanoparticles can impact biodistribution:
  – Size, surface charge, stability, density, crystallinity, surface characteristics, solubility
• Bioavailability of encapsulated and free drug may need to be assessed separately
• Multicomponent constructs may require ADME on each moiety
• Possibility of long term studies
Existing Guidance documents

• As the issues regarding nanoparticle-containing therapeutics are fully identified, all existing Guidance documents are applicable
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<tr>
<th>Topic Area</th>
<th>Guidance Title</th>
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<tr>
<td>CMC</td>
<td>Analytical procedures and methods validation: Chemistry, manufacturing, and controls documentation</td>
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<td>Comparability Protocols- Chemistry, Manufacturing, and Controls Information</td>
<td>2003</td>
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<td>Current Good Manufacturing Practice for Combination Products</td>
<td>2004</td>
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<td>Residual Solvent in Drug Products Marketed in the United States</td>
<td>2009</td>
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<td>Guideline on General Principles of Process Validation</td>
<td>1987</td>
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<td>Good Laboratory Practice Regulations: Questions and Answers</td>
<td>1998</td>
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<td>Liposome drug Products: Chemistry, Manufacturing, and Controls: Human Pharmacokinetics and Bioavailability, and Labelign Documentation</td>
<td>2002</td>
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<td>Process Validation: General Principles and Practices</td>
<td>2008</td>
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<td>Imaging</td>
<td>Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessment; Part 2: Clinical Indications; Part 3: Design, Analysis, and Interpretation of Clinical Studies</td>
<td>2004</td>
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<td>Procedural</td>
<td>Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies for Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products</td>
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<td>Early Development Considerations for Innovative Combination Products</td>
<td>2006</td>
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<td>Guidance for Reviewers: Pharmacology/Toxicology Review Format</td>
<td>2001</td>
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<td>Guidelines for Submitting Documentation for the Manufacture of and Controls for Drug Products</td>
<td>1987</td>
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<td>Guidelines for Submitting Supporting Documentation in Drug Applications For the Manufacture of Drug Substances</td>
<td>1995</td>
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<tr>
<td>PK/ADME</td>
<td>Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling</td>
<td>2006</td>
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<td></td>
<td>Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route</td>
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<td>Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients</td>
<td>2005</td>
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<td>Safety Testing of Drug Metabites</td>
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<td></td>
<td>Single Dose Acute Toxicity Testing for Pharmaceuticals</td>
<td>1996</td>
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A few examples of guidance that may be applicable to nanomedicine

• Combination products
• Liposome products
• Comparability protocols
Center for Drug Evaluation and Research
Current Activities

- Development of a MaPP on collection of information on nanomedicines in CMC reviews-completed
- Development of a comprehensive database of approved drugs and drugs under review-in progress
FY2011
FDA Science Budget Initiative and Request

• 1st explicit and dedicated support of science infrastructure and capacity in FDA’s budget
  – ~$25 million across agency
  – Major components
    Nanotechnology, Critical Path, Science Leadership, and others

• Emerging science
  – Nanotechnology review & safety
  – $7.33 million
Key Components of 2011 Nanotechnology Regulatory Science Initiative

- CORES Program (Collaborative Opportunities for Research Excellence in Science Program)
  - Enhance external and cross-Center activities
  - Support external research programs
- Laboratory Capacity to Assess Nanotechnology Products
  - Equip Core Laboratory Facilities
- Training and staff development
Characterization of Nanomaterials

- Define physical/chemical characteristics of nanomaterials that affect potency
- Define characteristics that impact safety

Biocompatibility

- Interaction with biological processes in tissues, fluids
- Pharmacokinetics

Safety

- Toxicokinetics
- *In vitro* toxicity test methods (*e.g.* cytotoxicity, genotoxicity)
- *In vivo* toxicity tests (*e.g.* 90-day, 2-yr)
Staff Training & Professional Development

- Invited Expert Presentations
  - Product Specific
  - Agency Wide
- Day Long Workshops
  - FDA Staff
  - International Experts Meeting
- Center Specific Activities
Nanotechnology Research Laboratory
Core Facilities: Locations

White Oak Campus and Surrounding Region
- CBER
- CDER
- CDRH
- CFSAN
- CVM

Jefferson Laboratories
- NCTR
- ORA
Summary

• A number of nanomedicine relevant products are approved and currently on the market
• The existing regulatory framework can accommodate the types of nanoparticle therapeutics under development and when needed, adapt to address new challenges
• Current published guidances may be applicable to nanoparticle therapeutics
• Staff are working on addressing the need for guidance documents that address nano-related issues as well as the regulatory science to bring to bear to this emerging technology
• FDA continues to encourage and participate in stakeholder dialogues
Closing Thoughts

International Partnerships
Acknowledgements